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Original Article

Comparison of Chemotherapy Alone with Chemotherapy Plus Rituximab for Treatment of Non-Hodgkins Lymphoma of All Ages and All Histological Subtypes

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Abstract

Introduction: The present day recommendations for treatment of non-Hodgkins lymphoma (NHL) patients is chemotherapy based on cyclophosphamide, doxorubicin, vincristine, and prednisolone with the addition of rituximab for those with cluster designation 20 positive tumors in selected ages and histologic subtypes. Rituximab has shown a favorable effect on the outcome of patients in these subsettings.

Purpose: We did a study to analyze the impact of rituximab added to the same chemotherapy on the outcome of NHL patients irrespective of age and histologic subtypes.

Methods: The case records of all NHL patients registered in our department from 2008 to 2013 were analyzed. The clinical, histopathological, and treatment details were noted. Comparison was done between patients having received rituximab-based chemotherapy with those who received chemotherapy alone.

Results: Of the 94 cases of NHL registered in our department over a 6 year period, 68 patients received chemotherapy in our department with different regimens. 36 patients received monoclonal antibody rituximab added to chemotherapy. The outcome of patients who received rituximab with chemotherapy with respect to complete response, event-free survival (EFS), and overall survival was significantly higher than those who received chemotherapy alone.

Conclusion: Addition of rituximab to chemotherapy increases the response rate, prolongs EFS, and overall survival in patients of all ages and histologic subtypes with NHL.

Key words: Chemotherapy, Event-free survival, Non-Hodgkins lymphoma, Overall survival, Response rate, Rituximab

INTRODUCTION

Non-Hodgkins lymphoma (NHL) incidence rates vary over the globe with highest rates in United States, Europe, and Australia, and lowest rates reported from Asia. The cause of most cases of NHL is unknown although several genetic diseases, environmental agents, and infectious agents have been associated with the development of lymphoma. The present day term NHL can no longer be considered as a single disease or an adequate diagnosis because as per the 2008 World Health Organisation classification of tumors of hematopoietic and lymphoid tissues, 86 distinct entities plus additional variants are included under the lymphoma category,[1] with more than 25 histologic subtypes of B-cell lymphoma having a wide range of biologic and clinical features.[2]

The cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen is the standard of care for patients with NHL,[3] but it induces complete responses in only 40-50% of patients, with 3-year event-free and overall survival rates of 30% and 35-40%, respectively.[4]

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In many studies,[5] addition of rituximab, a chimeric anti-cluster designation 20 (CD 20) monoclonal antibody to chemotherapy regimen of CHOP in patients with CD 20 positive tumors has significantly increased the rate of complete response, decreased the rates of treatment failure and relapse, and improved event-free and overall survival as compared with standard CHOP alone. However, these results have been seen only in elderly patients with newly diagnosed diffuse large B-cell lymphoma. Similarly also seen,[6] it is an improvement in overall response rates with rituximab added to chemotherapy for patients with low grade (follicular) lymphoma.

In this study, we compared chemotherapy alone with chemotherapy plus rituximab for CD 20 positive NHL patients of all ages and all histologic subtypes with an emphasis on the effect of rituximab on response, event-free survival (EFS), overall survival, and toxicity profile.

MATERIALS AND METHODS

Case records of all patients with a histopathological diagnosis of NHL registered in our department from 2008 to 2013 (both years included) were taken for the study. Details included registration number, age, sex, residence, clinical presentation, performance status, histopathological subtype, immunohistochemical analysis, type of treatment received, posttreatment outcome, and the last follow-up with special reference to response rates achieved and impact of rituximab on the EFS in these patients. All patients were subjected to a staging workup consisting of contrast-enhanced computerized tomography (CECT) of the neck, chest and abdomen, bone marrow biopsy, laboratory studies to determine renal, hepatic and marrow function, lactate dehydrogenase levels, and hepatitis serology. Cardiac function was evaluated by echocardiography. Only two patients had a positron-emission tomography (PET)-CT done in view of nonavailability of this modality in our state, even though all patients were made aware of the necessity of doing it. In 23 patients, disease was upstaged by CECT from clinical Stage I to Stage III and in two patients by PET-CT from Stage I to Stage III. Out of a total of 94 patients registered, only 68 patients were treated in our department plus 1 patient who had stage Is disease and was put on follow-up alone (total of 69 patients). Among those not treated, 15 patients absconded after registration only, 3 pediatric patients with Burkitt's lymphoma were referred to medical oncologist at the Sher-i-Kashmir Institute of Medical Sciences, and 7 patients had already received chemotherapy and/or radiotherapy at other centers before getting registered with us and all these absconded without receiving any treatment in our department.

Treatment

For these 68 patients, chemotherapy in different schedules was administered. The regimens included CHOP in 32 patients, rituximab, CHOP in 35 patients, and rituximab, high-dose systemic methotrexate, CHOP in 1 patient with testicular lymphoma. Patients treated with CHOP received the combination of 750 mg of cyclophosphamide/m^2 of body-surface area on day 1; 50 mg of doxorubicin/m^2 on day 1; 1.4 mg of vincristine/m^2, up to a maximal dose of 2 mg, on day 1; 16 mg of dexamethasone each on day 1 and day 2 (the equivalent of 100 mg of prednisone daily); 40 mg of prednisone m^2/day from day 3 to day 5. Patients treated with CHOP plus rituximab also received rituximab, at a dose of 375 mg/m^2, in two divided doses on day 1 and day 2 for all patients for first two cycles and for first four cycles for elderly and those with bulky disease. One patient received 3 g of methotrexate given intravenously over 6 h with leucovorin rescue. All the regimens were given for a total of 6 cycles at 3 weekly intervals. Although all eligible patients were offered rituximab, only 36 patients agreed and received it in combination with different chemotherapy regimes, whereas 32 patients received chemotherapy without rituximab.

Radiotherapy was used where ever it was indicated. Based on whether they received rituximab or not, they were grouped into two groups. Group I included those who did not receive rituximab with chemotherapy (nonrituximab group), and Group II included those who received rituximab with chemotherapy (rituximab group) (Table 1). Response to treatment and adverse events tumor responses were assessed after six cycles of chemotherapy as complete response, unconfirmed complete response, partial response, stable disease, or progressive disease according to the International Workshop criteria.[7] Complete response was defined as the disappearance of all lesions observed at diagnosis and the absence of new lesions. An unconfirmed complete response was defined as a complete response with the persistence of some radiologic abnormalities, which had to have regressed in size by at least 75%. Partial response was defined as the regression of all measurable lesions by more than 50% and the absence of new lesions. Stable disease was defined as a regression of any measurable lesion by 50% or less but without growth of existing lesions or the appearance of new lesions. Progressive disease was

Table 1: Distribution of patients according to treatment received

Total number of patients receiving treatment	Group I (nonrituximab group)	Group II (rituximab group)
68	32	36

defined as the appearance of a new lesion, any growth of the initial lesion by more than 25%, or growth of any measurable lesion that had regressed during treatment by more than 50% from its smallest dimensions.

All adverse events reported by the patient were collected from the case reports. An adverse event was defined as any adverse change from the patient's base-line condition, whether related to treatment or not. Each event was graded according to the National Cancer Institute Common Toxicity Criteria grading system.[8] Only Grade 3 and 4 events plus Grade 2 infections were recorded in detail, whereas Grade 1 and 2 adverse events were disregarded.

Statistical Analysis

Data were analyzed using SPSS version 20.0. Categorical variables were summarized as percentages. 95% confidence intervals were reported. Event-free and overall survival was assessed using Kaplan–Meier analysis. Mean survival time along with its 95% confidence interval was reported. The difference in survival times of CHOP versus Rituximab plus CHOP were analyzed by the log-rank test. Two-tailed *P*-values were reported, and a $P < 0.05$ was considered statistically significant.

RESULTS

The baseline characteristics of the patients in the two groups were compared (Table 2). There was no significant difference between the two groups in any clinical or pathological characteristic. The age distributions of the two groups showed that the majority of patients in both groups were <60 years and gender wise; the two groups were nearly equally matched.

The presence of B symptoms was noted in around 40% and 34% of patients of Groups I and II, respectively. Except one patient, whose histopathology was T-cell type, all others were B-cell lymphomas. Among the B-cell lymphomas, the majority of patients had diffuse large B-cell lymphoma followed by follicular type. All the patients were staged as per Ann Arbor staging system, and international prognostic index score was used for prognostication of patients in the two groups.

We followed the patients in the two groups regularly noting the time duration, for which they were event free after completing treatment. We observed that among patients of Group I, out of a total of 32 patients, 21 patients (66%) are disease free, alive, and on follow-up, whereas, in Group II, out of a total of 36 patients, 29 patients (81%) are disease free, alive, and on follow-up till cutoff date (December 2013). During this time, 11 events (relapse, death, and progression) were observed in Group I and 7 in Group II (34% and 19% of patients, respectively) (Table 3).

Event-free survival was slightly longer for patients of Group II than for Group I though the value did not have statistical significance ($P = 0.295$) (Table 4 and Figure 1). The difference in EFS between the treatment groups was attributable to the higher number of patients (nearly double) in Group I having disease relapse. There was benefit of rituximab, for all patients irrespective of bulk of disease, presence of B symptoms and age (data not shown).

In Group I, complete response was achieved in 53%, partial response in 9%, and stable disease in 3% of patients as compared with Group II where the complete response was achieved in 61%, partial response in 13%, and stable disease in 5%. Disease progression during treatment was reported in 1 patient each in Group I and II (Table 5). The rate of objective response was 62.5% and 75% in

Table 2: Characteristics of patients in the two groups

Characteristic	Group I (*n*=32) (%)	Group II (*n*=36) (%)
Age (years)		
≤60	22 (68)	23 (64)
61-70	06 (18)	09 (25)
>70	04 (12)	04 (11)
Gender		
Male	20 (62)	23 (64)
Female	12 (38)	13 (36)
B symptoms‡	14 (44)	12 (33)
Histopathology		
Diffuse large cell	25 (78)	29 (80)
Follicular	06 (19)	07 (19)
NK T-cell	01 (3)	0 (0)
Stage		
1	5 (15)	04 (11)
2	6 (19)	06 (17)
3	14 (44)	15 (42)
4	07 (22)	11 (30)
International prognostic index score		
Low (0-1)	09 (28)	07 (19)
Low intermediate (2)	14 (44)	13 (36)
High intermediate (3)	05 (16)	10 (28)
High (4-5)	04 (12)	06 (17)

‡B symptoms were defined as weight loss, fever, and night sweats. NK: Natural killer

Table 3: Status of patients in both groups at the end of study

Event	Group I (*n*=32)	Group II (*n*=36)
Alive and disease free†	21 (66)	29 (81)
Relapse†	06 (19)	03 (8)
Death†	04 (12)	03 (8)
Progression†	01 (3)	01 (3)

†Figures in parentheses are % age

Table 4: Mean event-free survival time in the treatment groups

Treatment	Mean	Standard error	95% confidence interval		*P* (Log-rank test)
			Lower bound	Upper bound	
CHOP	64.733	6.236	52.510	76.957	0.295
CHOP+rituximab	70.743	4.938	61.065	80.420	
Overall	69.268	4.031	61.368	77.167	

Table 5: Response to treatment in the two groups

Response	Group I (*n*=32)	Group II (*n*=36)
Complete response	17	22
Partial response	03	05
Stable disease	01	02
Progressive disease	01	01
Rate of objective response†	62.5% (45–79)	75% (60-89)
		P=0.2665

†Figures in parenthesis indicate 95% CI for rate of objective response. 95% CI for difference between rate of objective response among the two groups=9.19–33.09

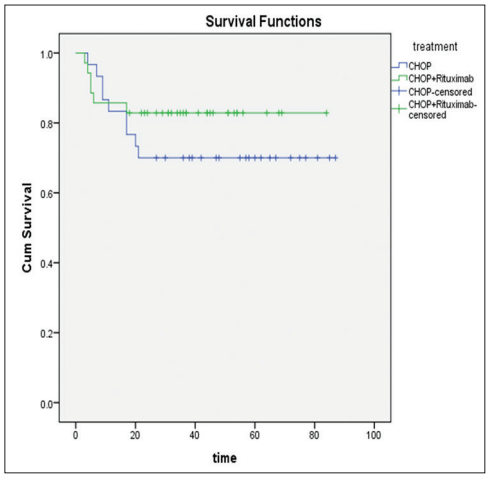

Figure 1: Event-free survival among 68 patients assigned to chemotherapy or chemotherapy plus rituximab

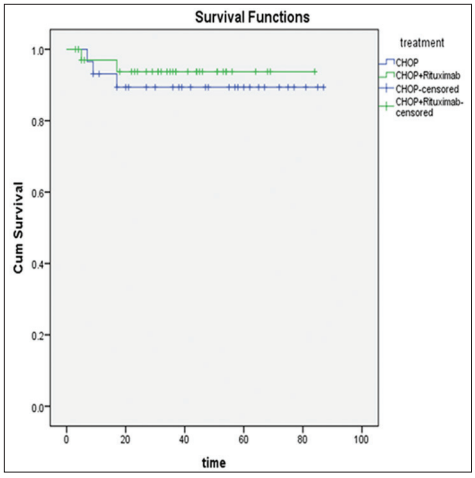

Figure 2: Overall survival among 68 patients assigned to chemotherapy alone or with rituximab

Group I and in Group II, respectively, with a $P = 0.2665$. Survival was longer for patients of Group II than for those of Group I although it was not statistically significant ($P = 0.599$) (Figure 2).

Adverse Effects

Table 6 presents all reported adverse events in each group. The Grades 3 and 4 adverse events were consistent with the expected toxic effects of CHOP chemotherapy and occurred with similar frequency in both groups. The occurrence of infusion-related events such as respiratory symptoms, chills, fever, and hypotension has been known with rituximab administration,[9-11] but we did not see such reactions because we divided the dose of rituximab over 2 days for first two cycles for all patients and for first four cycles in elderly patients and those with bulky disease. In addition, the infusion of rituximab was given slowly to all patients. The median fall of the neutrophil count after each cycle of chemotherapy was similar in both groups. The percentages of patients who required treatment with granulocyte colony-stimulating factor increased to a similar degree in each treatment group.

All adverse events reported by the patient or observed by the investigator were recorded. An adverse event was defined as any adverse change from the patient's base-line condition, whether it was considered related to treatment or not. Each event was graded according to the National Cancer Institute Common Toxicity Criteria grading system; higher numbers denote more severe toxicity.

DISCUSSION

In this study, we analyzed the data of NHL patients treated in our department with emphasis on the efficacy and safety of rituximab in combination with CHOP chemotherapy in patients of all ages and all histological subtypes. We found higher response rates, improved EFS, and overall survival (though not statistically significant) among patients treated with the combination of rituximab and chemotherapy irrespective of age and histologic subtype. The longer EFS in Group II was due to a lower rate of disease relapse among patients who had a complete response. Treatment with chemotherapy plus rituximab was well tolerated, and the incidence of severe or serious adverse events was no different from that in the chemotherapy alone group. The most common infusion-related effects

Table 6: Adverse events observed in patients treated with CHOP plus rituximab or CHOP alone

Neutropenia
Fever
Infection
Mucositis
Liver toxicity
Cardiac toxicity
Neurologic toxicity
Renal toxicity
Lung toxicity
Nausea or vomiting
Alopecia

CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone

seen almost universally were not experienced by our patients as we divided the dose of rituximab over 2 days for all patients for first two cycles and first four cycles for elderly and those with bulky disease. Furthermore, we gave the glucocorticoid component of CHOP regimen by intravenous route on first 2 days to act as a premedication for decreasing the chances and severity of infusion-related reactions. CHOP chemotherapy is considered a standard and less toxic regimen against which other regimens are to be compared. Hence, it is considered a first-line treatment for NHL patients and the outcome in this study with CHOP alone was the same as in other trails. Hence, the improved results in the group receiving CHOP with rituximab were actually attributable to the effects of rituximab.

CONCLUSION

In conclusion, the addition of rituximab to CHOP chemotherapy given for six cycles to newly diagnosed NHL patients of all ages and all histologic subtypes increases the rate of complete response, improves event-free, and overall survival as compared with standard CHOP alone. This improvement in outcome was achieved without any significant increase in clinical toxic effects probably due to modifications in the administration schedule of rituximab. Even though our results did not show a significant change statistically, but we believe that incorporating a greater number of patients and doing this study in a multicenter setting may achieve statistically significant and practice-changing results.

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